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Docket No.: C15043/91752DIV1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Continuing Application of :	)	
Paul N. HOLVOET and Désiré J. COLLEN	)	Parent Examiner: L. Cook
Serial No.: 10/802,709	)	Expected Art Unit: 1641
Filed: March 17, 2004	)	
For: ASSAYS, ANTIBODIES, AND STANDARDS FOR DETECTION OF OXIDIZED AND MDA-MODIFIED LOW DENSITY LIPOPROTEIN	)	

FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Mail Stop Amendment
Commissioner For Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicants wish to make of record the two documents identified below (clean copies and a Form PTO-1449 listing them are enclosed):

157. Holvoet P, Kritchevsky SB, Tracy RP, Mertens A, Rubin SM, Butler J, Goodpaster B, Harris TB. "The Metabolic Syndrome, Circulating Oxidized LDL, And Risk Of Myocardial Infarction In Well-Functioning Elderly People In The Health, Aging, And Body Composition Cohort." *Diabetes*. 2004; 53(4): 1068-1073.

158. Sigurdardottir V, Fagerberg B, Hulthe J. "Circulating Oxidized Low-Density Lipoprotein (LDL) Is Associated With Risk Factors Of The Metabolic Syndrome And LDL Size In Clinically Healthy 58-Year-Old Men (AIR Study)." *J Intern Med*. 2002; 252(5): 440-447.

REMARKS

The relevance of each is set forth below.

157. Holvoet P (one of the present inventors), Kritchevsky SB, Tracy RP, Mertens A, Rubin SM, Butler J, Goodpaster B, Harris TB, "The Metabolic Syndrome, Circulating Oxidized LDL, And Risk Of Myocardial Infarction In Well-Functioning Elderly People In The Health, Aging, And Body Composition Cohort," *Diabetes*. 2004; 53(4): 1068-1073, concerns a study that was conducted to establish the association between the metabolic syndrome and oxidized LDL (oxLDL) and to determine the risk for coronary heart disease (CHD) in relation to the metabolic syndrome and levels of oxLDL. OxLDL was measured in plasma from 3,033 elderly participants in the Health, Aging, and Body Composition study. The metabolic syndrome was associated with higher levels of oxLDL due to a higher fraction of oxLDL, not to higher levels of LDL cholesterol. Individuals with the metabolic syndrome had twice the odds of having high oxLDL compared with those not having the metabolic syndrome, after adjusting for age, sex, ethnicity, smoking status, and LDL cholesterol. OxLDL was not an independent predictor of total CHD risk. However, those with high oxLDL showed a greater disposition to myocardial infarction (relative risk 2.25, 95% confidence interval 1.22-4.15). The authors concluded that the metabolic syndrome, a risk factor for CHD, is associated with higher levels of circulating oxLDL that are associated with a greater disposition to atherothrombotic coronary disease. (Abstract) "[T]he metabolic syndrome is associated with high risk for atherosclerotic disease, a process thought to involve LDL oxidation ..." (page 1068). A monoclonal antibody (mAb-4E6) was used to measure plasma oxLDL levels (page 1069). "[A]n inverse relationship between HDL cholesterol and circulating oxLDL has been shown in healthy middle-aged men ..." (page 1072; citation omitted). "[T]hese data support the hypothesis that an increase in oxLDL reflects plaque instability" (Id.). "Our data also further support the predictive value of the metabolic syndrome for CHD and suggest that baseline levels of oxLDL add prognostic information concerning future risk for MI" (Id.).

158. Sigurdardottir V, Fagerberg B, Hulthe J, "Circulating Oxidized Low-Density Lipoprotein (LDL) Is Associated With Risk Factors Of The Metabolic Syndrome And LDL Size In Clinically Healthy 58-Year-Old Men (AIR Study)," *J Intern Med.* 2002; 252(5): 440-447, concerns a study conducted to test the concept that the atherogenic effect of the metabolic syndrome may be mediated through the increased occurrence of small LDL-particles which are easily modified to atherogenic oxidized LDL (ox-LDL). The study examined the association between circulating ox-LDL, LDL-particle size, and the metabolic syndrome. Ox-LDL was measured by ELISA (using monoclonal antibody mAb-4E6). ox-LDL significantly correlated to factors constituting the metabolic syndrome; triglycerides, plasma insulin, body mass index (BMI), waist-to-hip ratio, and HDL. Ox-LDL correlated also to LDL-particle size, Apo-B, LDL, Apo A-1, and heart rate. The authors found that the metabolic syndrome was accompanied by high plasma ox-LDL concentrations compared to those without the syndrome. Ox-LDL levels were associated with most of the risk factors constituting the metabolic syndrome and were also related to small LDL-particle size. The authors stated that, to their knowledge, the present study was the first to demonstrate that circulating ox-LDL levels are associated with small LDL-particle size in a population representative sample of clinically healthy middle-aged men. They also noted that the high degree of intercorrelation amongst several factors makes it difficult to clarify the independent role of any specific factor. (Abstract) "The results fit well into the current concept of ox-LDL as a key mechanism in the development of atherosclerosis" (page 443). The authors note that small dense LDL particles tend to be easily oxidized and that they have low affinities for the LDL receptor (pages 443-444). "There are only few previous studies which have shown a relationship between increased levels of circulating ox-LDL and cardiovascular risk factors, such as hypercholesterolemia, BMI, type 2 diabetes and age ..., as well as triglycerides, HDL and LDL ... in selected populations at high risk. However, another study, using a different monoclonal antibody (anti-OxPC), did not show any correlation with major risk factors for CHD, such as hyperlipidemia, hypertension and cigarette smoking ...." (pages 444-445; citations omitted)

* * *

These documents are believed to be of moderate relevance; however, the Examiner's independent consideration of them and of their relevance is respectfully requested. The Examiner is also requested to initial and return copies of the accompanying PTO-1449 Form to evidence such consideration.

This FIRST SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT is being filed in accordance with the provisions under 37 CFR § 1.97(b)(3) based on applicants' belief that it is being filed before the mailing of a first Office Action on the merits. Thus, a fee is not required for filing this paper; however, if any fee is owed, please charge the fee to our Deposit Account No. 02-4467.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Mail Stop Amendment, Commissioner For Patents, P.O. Box 1450, Alexandria, VA 22313-1450

on June 15, 2004
(Date of Deposit)

Stephen P. Gilbert
Signature

Respectfully submitted,

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PATENT & TRADEMARK OFFICE

Form PTO-1449 (Rev.)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO.	SERIAL NO.
	INFORMATION DISCLOSURE STATEMENT BY APPLICANT	C15043/091752 (Div)	10/802,709
		APPLICANTS Paul N. Holvoet and Desire J. Collen	
	(Use several sheets if necessary)	FILING DATE March 17, 2004	GROUP Not Yet Assigned

U.S. PATENT DOCUMENTS

Examiner Initial	Cite No.	U.S. Patent Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation	
							Yes	No

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Holvoet P, Kritchevsky SB, Tracy RP, Mertens A, Rubin SM, Butler J, Goodpaster B, Harris TB. "The Metabolic Syndrome, Circulating Oxidized LDL, And Risk of Myocardial Infarction In Well-Functioning Elderly People In The Health, Aging, And Body Composition Cohort." *Diabetes.* 2004; 53(4): 1068-1073.
		Sigurdardottir V, Fagerberg B, Hulthe J. "Circulating Oxidized Low-Density Lipoprotein (LDL) Is Associated With Risk Factors of The Metabolic Syndrome And LDL Size in Clinically Healthy 58-Year-Old Men (AIR Study)." *J Intern Med.* 2002; 252(5): 440-447.

EXAMINER	DATE CONSIDERED

Examiner: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

RS1161165